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TITLE: Microtubule Abnormalities Underlying Gulf War Illness in Neurons from Human-Induced Pluripotent Cells

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14. ABSTRACT The study plan is to develop immortalized cultures of cells from the blood of veterans who are suffering from Gulf War Illness (GWI). A simple blood sample is taken from the soldier, and then transduced, using reliable established methods, to make the cells pluripotent. The pluripotent cells lines can then be treated with growth factors to differentiate them into a number of different cell types including neurons. The investigators will develop these cell lines from veterans of the Gulf War who got sick and also from veterans who did not get sick, so the two can be compared. Other scientists studying GWI will be able to use the cell lines for their own studies, which will maximize the effort of the biomedical community to rush medicines and treatment regimens to the veterans who are suffering. For the two-year proposed study, the first year has been devoted to establishing the cell lines, as well as early phases at testing microtubule-based therapies for restoring cellular functions to normal in neurons derived from human pluripotent cells exposed to Gulf War toxins.						
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1 **INTRODUCTION:** Gulf War Illness (GWI) is thought to have its origins in exposure of soldiers serving in the 1991 war to various neurotoxicants, including pesticides, anti-nerve gas pills, and low level nerve gasses including sarin/cyclosarin. Studies to date have shown deficits in the movement of proteins and organelles within nerves by the process known as axonal transport, as well as aberrations in microtubules, which are the structural railways for axonal transport. Given the importance of microtubules, damage to them is suspected as a primary cause of neurodegeneration in GWI, as it is in many neurodegenerative diseases. Further investigation into this matter has a strong possibility of yielding effective treatment strategies. Animal models may not suffice to provide the needed insights, and therefore efforts to generate pluripotent cell lines from the veteran themselves will enable studies on microtubules to move forward more effectively, and will also provide a toolkit for other GWI researchers to use in the future, as the cell lines will be immortal once they are generated. The hypothesis is that exposure of neurons and/or neuroinflammatory cells to GW toxins caused long-lasting microtubule defects in neurons, and that these defects lead to a loss of microtubule mass, a change in the proportions of stable and labile microtubule mass, and/or flaws in the lattice of the microtubule that lead to abnormalities in how molecular motor proteins and other microtubule-related proteins interact with the microtubule. One objective is to develop new immortal lines of pluripotent cells derived from the blood of GW veterans themselves, so that the microtubule hypothesis (as well as other GWI hypotheses beyond the present proposal) can be tested. The other objective is to assess whether available microtubule-active drugs can correct these abnormalities and provide treatments for GWI.

2 **KEYWORDS:** *microtubule, neuron, Gulf War Illness, hiPSC*

3 **ACCOMPLISHMENTS:**

What were the major goals of the project?

- Aim 1. Develop human neurons or glial cells derived from human induced pluripotent stem cells (hiPSCs), originating from GW veterans with GWI and healthy GW veteran controls.
- Aim 2. Develop a microtubule-based strategy to treat impaired nervous system in GWI.

What was accomplished under these goals?

- 12 GW veterans were recruited (8 GWI cases, 4 controls) and blood samples were obtained. 4 hiPSC lines were developed and frozen for experimental use.
- In the meantime, while the cell lines were being generated, preliminary experiments on the microtubule work was conducted on human cell lines obtained commercially. Plan are to include some of these preliminary studies on human neurons in a manuscript to be submitted by the middle of October 2016 that mainly includes work on rat neurons funded by the GWI Consortium grant.
- Having completed the preparation of the cell lines, a manuscript describing their preparation and the rationale behind using them to study GWI has been written

and will be submitted by middle October 2016 so that the greater GWI community will be aware of the bank of hiPSCs available for collaborative projects.

What opportunities for training and professional development has the project provided?

- Nothing to report

How were the results disseminated to communities of interest?

- Nothing to report this cycle, but plans are underway to submit the two manuscripts indicated above for publication in high visibility journals.

What do you plan to do during the next reporting period to accomplish the goals?

- During the next funding period, Aim 2 will be pursued, precisely as proposed.

- 4 **IMPACT:** *Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?

- There is now a bank of hiPSCs available to the GWI community to use for testing of mechanistic hypotheses and therapies.
- Pre-clinical studies on mechanism and therapy for GWI have been limited until now to animals that are imperfect models for human disease. These new human cell lines will provide a major resource for GWI researchers.

What was the impact on other disciplines?

- Nothing to report

What was the impact on technology transfer?

- The resource of GWI hiPSC cells will not be used for commercial profit but will instead be made available for collaborative projects with GWI investigators.
- **What was the impact on society beyond science and technology?**
 - Nothing to report

- 5 **CHANGES/PROBLEMS:**

Changes in approach and reasons for change

- Nothing to report

Actual or anticipated problems or delays and actions or plans to resolve them

- *Nothing to report*

Changes that had a significant impact on expenditures

- Nothing to report

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

- Nothing to report

Significant changes in use or care of human subjects

- Nothing to report

Significant changes in use or care of vertebrate animals.

- Nothing to report

Significant changes in use of biohazards and/or select agents

- Nothing to report

- 6 **PRODUCTS:** *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."*
- Two manuscripts, as described above will be submitted for publication by middle October 2016.

Website(s) or other Internet site(s)

- The GWI Consortium that gave rise to the project has a website that will be used in the future to disseminate the progress and availability of the hiPSC lines.

Technologies or techniques

- Nothing to report

Inventions, patent applications, and/or licenses

- Nothing to report

Other Products

- The bank of hiPSC cells has been produced

7 **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

What individuals have worked on the project?

- Peter Baas, Kimberly Sullivan, Liang Qiang: No change

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

- Nothing to report

What other organizations were involved as partners?

- **Organization Name:** Boston University School of Public Health
- **Location of Organization:** 715 Albany Street, Boston, MA
- **Partner's contribution to the project**
 - **Financial support** - none to report
 - **In-kind support** - None to report
 - **Facilities** – BUSPH stem cell center reprograms blood cells at expert facility, blood draws occur at BU general clinical research unit, Subject recruitment occurs at BUSPH.
 - **Collaboration** – Subject recruitment, blood draws and reprogramming of stem cells occurs at BU.
 - **Personnel exchanges** - subject recruitment is done at BUSPH site with BUSPH research assistant.
 - **Other** – none to report

8 **SPECIAL REPORTING REQUIREMENTS**

COLLABORATIVE AWARDS

- n/a

QUAD CHARTS

- n/a

9 **APPENDICES**

- n/a